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A CONTRIBUTION TO THE STUDY OF THE MORPHOLOGY OF ADIPOSE TISSUE. By H. Batty Shaw, M.D., *Assistant Physician to University College Hospital.*

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In studying the literature dealing with the development of fat, it very soon becomes obvious that opinions in the past were very much divided, and two important views were held. On the one side there were observers who insisted on the belief that fat cells were developed from special cells set aside for the purpose of developing and storing fat; on the other, that fat cells were not specific structures, but that fat was stored up in cells which were everywhere widespread, and were constituents of connective tissue.

Todd and Bowman (1), writing in 1845, definitely state that adipose and areolar tissues should be looked upon as altogether distinct and independent tissues. In 1856 Kölliker described large polygonal cells with a finely granular but otherwise clear protoplasm occurring in the mesentery and around the kidneys in kittens one, two, or three days old; these cells were noticed a few days later to contain fat globules. Kölliker (2) considered that these polygonal cells were primitive, and that they formed definite structures which, from their appearance, should be considered as glands, and such he named them. Nearly thirty years later Kölliker (3) reaffirmed his views, stating that many fat lobules are produced from special kinds of connective tissue cells. He also asserts that the individual fat cells can be reconverted into connective tissue cells, and these again into fat cells.

In 1866 Czajewicz (4) published observations on fat formation, and was of the opinion that fat was laid down in connective tissue cells, but not in any special group of them, and that in cases of excessive feeding even the epithelial cells of the mesentery could be filled with fat globules. In 1870 Flemming (5) published two papers on the development of fat in the subcutaneous tissue and in the mesentery. In these two papers he has shown most conclusively that, in the situation examined, fat is deposited in simple fixed connective tissue cells. As a result of starvation, the fat was removed from these cells, and the original simple connective tissue cells were reproduced. In fig. 25 of plate viii. he shows a cell which has considerable resemblance to cells whose description will be given later.

In the same year Toldt (6) emphatically declared in favour of definite fat-forming organs. These he found in kittens and young rabbits under the skin, between the muscles, in the neck and around various joints and near the kidneys; the cells of these glands, before fat was formed within them, were very large, of variable form, and finely granular. He found the cells of the 'fat bodies' of frogs under conditions of insufficiency of food, to consist entirely of similar cells. The highly developed capillary system which formed a network through these 'fat glands,' especially attracted his attention.

In 1873, Klein (7), as a result of his investigations, considered that the fat lobules of the omentum and mesentery were transformed peri-lymphangeal lobules, and that, in agreement with Toldt, fatty tissue is a special form of glandular tissue. Waldeyer (8) concluded that the fat cells were formed according to Flemming's views, *i.e.* from simple fixed connective tissue cells, but that Toldt also was right in his assertion, that fat was laid down in special cells rich in protoplasm. In addition Waldeyer observed fat formation in the wandering 'plasma' cells which have since been known under his name. Toldt's views received further confirmation from Ranvier (9), whose observations were carried out in new-born rabbits and in calves. He noticed, as other observers had done, the close association of fat cells with blood-vessels, and that these cells near the vessels were more loaded with fat than those more remote—the latter, indeed, being quite free from fat. Ranvier inclined to the opinion that

each cell in question should be considered as a unicellular gland; he does not follow Toldt in naming the various fat accumulations 'fat glands.' In 1876 Flemming (10) again discussed the question. In his earlier papers he agreed with other observers that fat cells were closely associated with small blood-vessels, but in the later work he describes small groups of fat cells occurring, especially in young rodents, quite independent of vessels. He lays great stress upon the point, because earlier observers had quoted this close relationship of blood-vessels and cells as a strong support of the 'glandular' nature of the cells concerned. Flemming failed to find any sharp boundary between the fat cells and the other cells of the adjacent connective tissue.

Two years later an important paper was published by Löwe (11), who stated the three prevailing views as to the origin of fat droplets in cells. The first view was only mentioned to be dismissed for want of evidence, namely, that fat droplets were absorbed from the intestine and carried by the blood and implanted as such in certain cells. The second view was Flemming's 'impletion' theory; fat circulated in the blood as a watery solution, the blood then bathes certain connective tissue cells with the solution, and then these cells elaborated fat within themselves from the fluid supplied; if such cells began to atrophy, then the fat was again converted and carried off by the blood stream. The third theory was that of Toldt, the so-called 'ontogenetic' theory, by which it was supposed that certain special cells collected into glands had a special power of elaborating fat from the various materials of the blood plasma. He doubts Flemming's theory, because he says in the fat accumulations, described by others as glands, it is so very rare to be able to demonstrate connective tissue cells in the earliest stage of fat impletion. Löwe concludes that there are specific fat cells, and that they are primarily wandering cells.

Mr and Mrs Hoggan's (12) observations confirmed Flemming's views. Fat was not deposited in special fat cells or glands, but in branched cells, which they think, however, are wandering cells, whereas Flemming asserts that they are fixed. They studied fat formation as well as fat atrophy in cells of the broad ligament of rodents. In the former case they think fat is deposited in cells as single or many globules,

according to varying conditions of food supply, etc.; but that when fat cells atrophy, each fat globule does not break up into many globules, but remains one until it has quite disappeared.

In the same year Flemming's (13) fourth paper appeared. He still adheres to his former views, and shows that if an animal be starved sufficiently and sections be made of tissues existing in places where fat had originally been laid down, not only will the fat cells have disappeared, but the supporting capillary system will have atrophied too, and he figures atrophying capillaries; this, he says, is quite contrary to our conception of a gland, for the parenchyma should persist.

So far the review of the literature on the subject has been made with the object of getting clearer ideas as to the origin of fat cells. The careful observations made by Flemming in his four papers certainly establish the fact that fat is largely laid down in fixed branched connective tissue cells; it is possible that other cells are sometimes concerned in the process, but always to a much less degree, whether they be plasma cells described by Waldeyer, or the wandering cells described by Mr and Mrs Hoggan.

The next observers whose work remains to be reviewed, have called attention to the large polygonal, richly protoplasmic, cells first mentioned by Kölliker.

In 1883 Ehrmann (14) observed polygonal finely granular cells, which occasionally contained many fat globules, and he revives the name originally given to these cells by Ludwig, and calls them mulberry cells. Ehrmann is opposed to calling fat cells 'glandular,' and thinks they are probably wandering cells, as described by Waldeyer.

Bobritzky (15), in 1885, investigated fat formation in various mammals and arthropods, and thinks that fatty tissue develops out of a special element, and not from mere connective tissue cells; he describes rounded cells with granular protoplasm occurring in young embryos, in places in which eventually fatty tissues is laid down, and he says that these cells can be changed into wandering cells very similar in appearance to Waldeyer's plasma cells.

Poljakoff (16) has published observations on the subcutaneous tissues of white rats, and describes large spherical cells which in

some cases actually help to form the walls of the capillaries, and which, by a gradual transition, become fat-forming cells. He shows the effect of atrophy and inflammation upon these cells, but does not investigate the development. According to Poljakoff, Waldeyer's cells, Ranvier's flat cells, Ehrmann's mulberry cells and fat cells, are merely modifications of one embryonic cell found in connective tissue. According to Poljakoff, all the fat-containing cells are in close proximity to vessels; but this is in opposition to Flemming's observation above mentioned, namely, that fat cells can develop quite independently of proximity to vessel walls. Poljakoff says these cells may take on amœboid movements.

Finally, in 1890 Metzner (17) published a paper, and inclines to the idea that there are special cells set apart for fat-formation, and that Flemming missed them by not examining early embryos. Metzner examined young animals and found a peculiar tissue in the axilla and thorax, and around the kidneys, which was quite free from fat, and consisted of large polygonal cells with granular protoplasm. He says these cells belong to connective tissue, but that they are not identical with connective tissue cells. He also starved animals, but found that developed fat could not be entirely got rid of, because the animals died before such a stage could be reached.

Despite all attempts to prove the existence of special cells set aside for the formation of fat, it must be admitted that the evidence is slight; no one, so far, has succeeded in getting rid of all the fat of the body of an animal and finding granular polygonal cells left massed together; all that is visible is connective tissue. In the examination of several cases of marasmus in infants, I have never been able to find such polygonal highly protoplasmic cells, nor in the development of fat in the body is it possible to demonstrate these large cells acting as precursors of fat-formation. The observations carried out and giving rise to this paper have been made on human fœtuses from the fourth month till maturity, and on infants and older subjects of all ages.

In the adult human being adipose tissue has the ordinary characters ascribed to that tissue. It consists of large cells containing fat in the form of single globules, which are encircled

by a thin envelope of protoplasm, the presiding nucleus being dislocated from the centre of the cell to some spot at the periphery, giving rise to the well-known signet ring appearance. In the human embryo of about the fifth or sixth month, the fatty tissue present will be seen in the form of small yellow pellets beneath the skin; a few weeks later obvious accumulations are visible in the omentum, around the kidneys, in the axillæ, groins, under the parietal pleura, and in other places. In the case of the subcutaneous accumulation, the fat is deposited in connective tissue cells, usually as a single globule, which enlarges till it produces, by its growth, a much larger cell than the original; occasionally, however, the connective tissue cells are seen to possess more than one globule of fat, and there may be five or six; but eventually the same uniglobular fat cells are produced by the coalescence of the smaller globules. In the other sites mentioned, it is much more common for the fat to be deposited in the connective tissue cells in temporary drops, thus producing the appearance which Ludwig compared to that of a mulberry. These 'mulberry' fat cells, as well as those already mentioned as occurring in the subcutaneous tissue, tend eventually to assume the uniglobular form.

Towards the end of fœtal life, a section of fat taken, say, from beneath the pleura, or from the axilla, will show many mulberry as well as uniglobular fat cells. Often there is visible a very well marked capillary system, the small vessels lying between adjacent cells. In addition, however, there will be seen cells whose characters are quite different from the fat cells amongst which they lie. They are rarely as large as the fat cells, but the nucleus is very similar; the great distinction, however, is the absence of fat globules; the protoplasm is finely granular, often is quite free from fat globules, even of the smallest dimensions, and is readily stainable. The contour of such cells is largely dependent upon the proximity of other cells; where they lie comparatively free from the pressure of adjacent cells, they are roughly spherical; often, however, so tight is the packing of the tissue in which they lie that they assume a polygonal form. After birth in the human subject, a very striking change takes place; in the case of two infants who died at the ages of two and three weeks respec-

tively, sections of the subpleural tissue, which in older subjects was found to consist of simple fat, showed that uniglobular fat cells were the exception; 'mulberry' fat cells were far less frequently met with, and the above-mentioned polygonal cells were visible in every field, free in many cases from any vestige of fat, occurring not singly but in irregular groups, which were interspersed amongst groups of cells possessed of fat globules, more or less 'mulberry' in form. The protoplasm of these cells was extremely abundant, and a first glance of the tissue

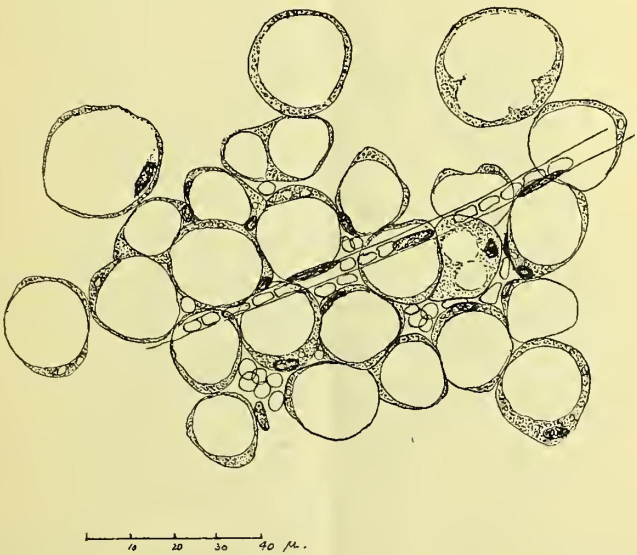

FIG. 1.—Section taken from subpleural tissue of a fœtus of the seventh month. Most cells in this drawing show single globules of fat.

would suggest a likeness to a layer of squamous epithelium, so extensive is the area of protoplasm as compared with the size of the nucleus. A closer observation, however, would at once disclose the fact that here, as in other sections of adipose tissue examined, there is an abundant capillary network; the capillaries seem to cut notches in the contour of the cells occupying a position between adjacent cells, very much like that of the bile canaliculi between the liver cells. In this study it was a matter of great good fortune that the cause of death in the two subjects first described was asphyxia from overlying: the result

has been that the minutest capillaries are found packed full of red corpuscles, which so readily take up the eosin stain.

In examining older infants than the last two, a reversion is met with to the type of tissue seen in fœtuses of six, seven, eight, or nine months of age, *i.e.* there is an abundance of uni- and multi-globular fat cells, and only here and there can a 'pleo-protoplasmic' cell be discovered. Subjects of six years and older show the ordinary uniglobular fat cells.

FIG. 2.—Section taken from subpleural tissue of a fœtus of the ninth month. No simple fat cells visible; most are 'mulberry' like; one is seen quite free from fat.

The illustrations shown in this description are taken from sections of subpleural tissue, as that is the tissue which was preserved with the greatest care in the first case; unfortunately, samples of fat were not taken from other localities of the same individuals, to see whether similar changes went on in all parts. In many cases perirenal and axillary fat have been examined, and show, generally, changes very similar to that above described.

Seeing that the above change in fat cells occurs shortly after birth, and in turn gives place to a further development of fat cells in a week or two, it may well be thought to be due to a

sudden call upon the stored fat, incident upon the passage from

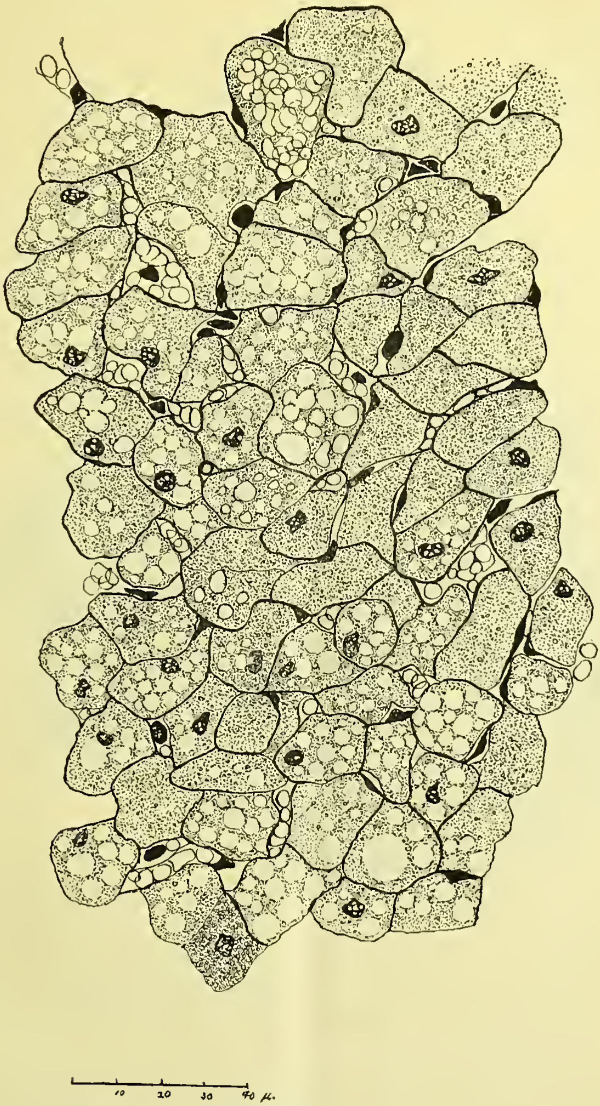

Fig. 3.—Section taken from the subpleural tissue of an infant two weeks old. This sketch shows the cells in their 'pleo-protoplasmic' condition; also abundant capillary network with nuclei of capillary epithelium. Some cells are 'mulberry' like in appearance.

intra-uterine to an independent existence. That this is not so,

however, is proved by the fact that in some of the lower mammals a similar condition of fat cells is met with at, or even before birth, the 'pleo-protoplasmic' condition being found in fat in all localities, though not necessarily to an equal degree in each locality. Again, it may be thought that all fat cells, when

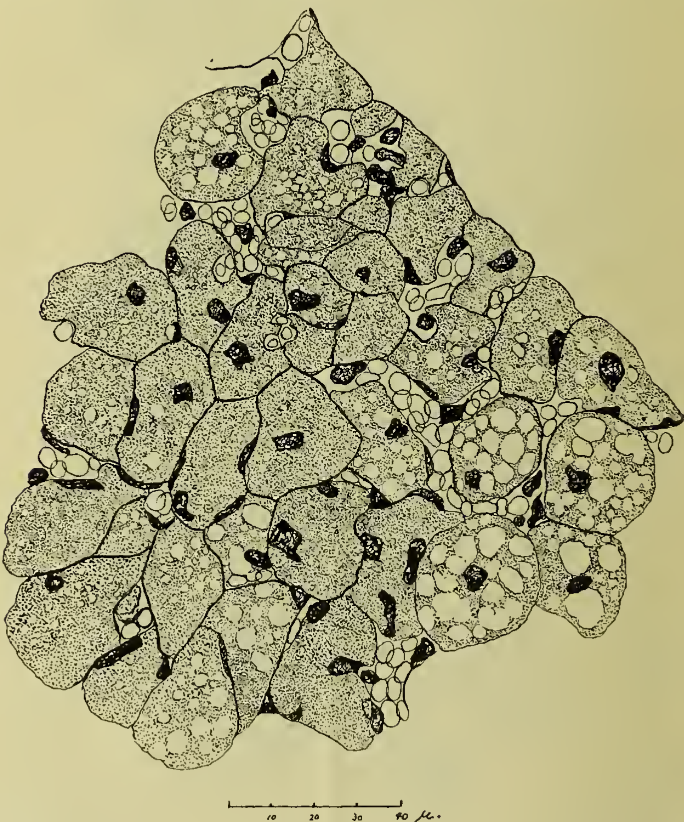

FIG. 4.—Section taken from the subpleural tissue of an infant three weeks old. The appearance is the same as that of infant two weeks old.

deprived of their fat globules, would assume the appearance met with in the young infants above described, but the objections to this view are, that in the numerous starvation experiments that have been made, similar cells have not been met with; the starvation not only removes the fat, but the protoplasm as well, and the cells rapidly assume the characters of connective

tissue cells; further, in studying the development of fat, besides being convinced that Flemming is right as to the beginning of fat formation, by the development of fat globules in connective tissue cells, it is a fact that the pleo-protoplasmic stage above referred to is never met with; it is not a necessity for the deposit of fat in a cell that such cell should be abundantly supplied with protoplasm; in the omentum, for example, fat may be seen

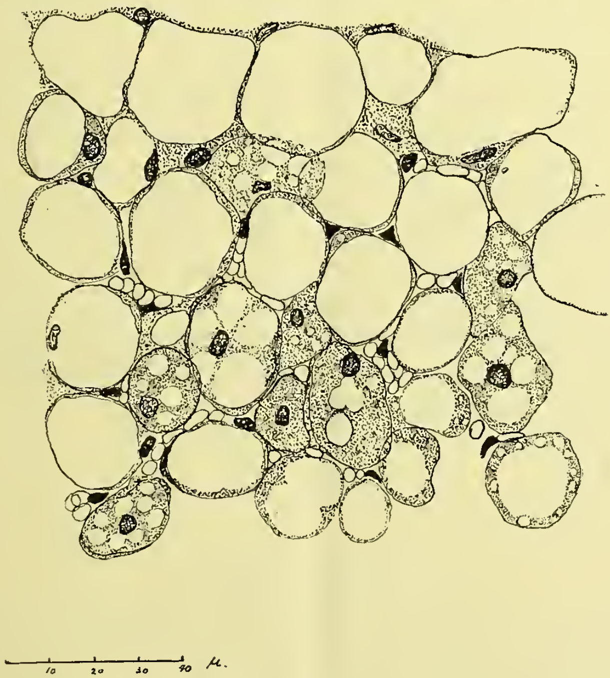

FIG. 5.—Section taken from subpleural tissue of an infant eleven months old. Shows many simple fat cells, others of the 'mulberry' type; one in the lower part quite free from fat.

deposited as two or three globules in cells whose protoplasm is quite scanty.

The methods adopted in this study have been purely histological; the fixation of the tissues in Flemming's solution has repeatedly proved that the globules under examination were fatty. Exceptions, however, were met with, *e.g.* some globules appeared to be other than fatty, as they did not show the same effect at all; other globules showed an incomplete effect,

possibly due to the transition to fat. With further investigation, it may be possible to make out some chemical differences in these cells whilst they are in this stage of metamorphosis. It is quite easy in the dissection of the axilla of a new-born child, to separate fully developed fat from fat showing this change—the latter tissue looks more pink, appears firmer, and does not adhere to the scalpel as fat does.

In conclusion, the above study points to the suggestion that much of the discussion as to the origin of fat has been brought about by the fact that Kölliker, and those who accepted his views, had not traced fat to a sufficiently early period of life. Had they done so they must have accepted Flemming's statement that there were no special 'fat glands,' and that all fat commenced as deposits in connective tissue cells. Kölliker, struck with the appearance of fat cells such as has been described above, looked upon the appearance as that of a gland, instead of considering it as merely a metamorphosis occurring in the fat of the body reaching its maximum at or before birth in some quadrupeds, and in the infants above-mentioned some two or three weeks after birth.

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